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10/537,258	11/03/2005	Paul Goldsmith	0380-P03627US0	1424

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EXAMINER	
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1632	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/537,258	GOLDSMITH ET AL.	
	Examiner	Art Unit	
	Valarie Bertoglio	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *05 June 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-22 and 24-42* is/are pending in the application.

4a) Of the above claim(s) *1-22,24-29 and 36-38* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *30-35,39-42* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on *N/A* is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *01/17/2006*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Applicant's election with traverse of Group V, claims 30-35 as they are drawn to a method of determining whether at least two agents affect activity of a treatment on a fish in the reply filed on 06/05/2007 is acknowledged. The traversal is on the ground(s) that multiple groups have common method steps and it is these method steps that define a contribution over the prior art. This is not found persuasive because the method steps of each invention are different. Claim 30 requires treatment of fish with multiple agents to determine the synergy of the agents in affecting a phenotype of the fish wherein the phenotype was induced by an unrelated treatment. Claim 1 is directed to screening for a single substance (or a first gene) that affects an aspect of behavior or physiology in a fish that is a result of a treatment or a transgene. Determining synergy is different than determining the effect of a single substance. To determine synergy is to compare individual treatment with a combination of treatments to determine of the combination exacerbates the individual treatment effects. Applicant also argues there is no search burden. However, search burden is not germane to lack of unity practice. Furthermore, it is noted that there is no requirement in MPEP 800 or 1800 that requires an examiner in a National Stage application to follow the lack of unity practice of the PCT examiner. If applicant knows of such a requirement, they are invited to point to such in the MPEP or other guiding authority.

Claims 36-42 were not considered in the restriction requirement, as the claims were unclear. Applicant has amended the claims. Claims 36-38 are distinct from the elected Group V because they are related to a method of identifying a single substance that reduces a phenotypic effect of a treatment, or decreases the side-effect profile of a drug, whereas Group V is a distinct method drawn to determining synergy between agents on a phenotype. Claims 39-42 have been amended to depend from claim 35 and are therefore grouped with Group V. However, how these claims relate to the method steps of claim 35 is wholly unclear (see rejection under 112, 2nd paragraph below).

Claim 23 is cancelled. Claims 1-22 and 24-42 are pending. Claims 1-22, 24-29, and 36-38 are withdrawn. Claims 30-35 and 39-42 as they relate to a model fish subject to a treatment that affects behavior or physiology of said fish, and methods of screening synergy of agents using said fish, are under consideration in the instant office action.

Claim Objections

Claim 35 is objected to because of the following informalities: It appears the term "subjerating" in line 1 is a typographical error or misspelling. Appropriate correction is required.

Claim 35 is objected to because of the following informalities: Claim 35 reads on non-elected subject matter. Specifically, the claim is drawn to use of transgenic fish in screening, which is patentably distinct from the elected invention. Applicant is required to remove the non-elected subject matter from the claim prior to allowance.

Claims 31-35 and 39-42 are objected to because of the following informalities: Referring to "The" subject of a previous claim, rather than "A", is proper format for a dependent claim. Accordingly, "A method" in claims 31-35 and 39-42 should read "The method". Appropriate correction is required.

Specification

The disclosure is objected to because of the following informalities: It appears the term "Addictive" is misspelled at page 15, line 25.

Appropriate correction is required.

Claim Rejections - 35 USC § 112-2nd paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 30-35 and 39-42 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 30 is unclear in a number of respects. Claims 31-35 and 39-42 depend from claim 30.

1) The preamble refers to determining whether two "substances, drugs, genes or drug targets" affect a phenotype. However, the body of the claim refers to subjecting fish to a test substance or mutation. It is not clear how the test substance or mutation relates back to "drugs, genes, or drug targets".

2) The phrase "or activity or effect of a physiological function or behavior" in the preamble is unclear in how it relates to the act of determining. The claim is drawn to determining synergy between substances or substances and a mutation on a physiological function or behavior. The frequency of the occurrence of the term "or" in the preamble renders it unclear.

3) Claim 30 fails to provide clear antecedent basis for each of the fish. The claim would be more clear if in the 'subjerating' step, section (i) were to end with "to provide a mutated fish". In the comparing step, it should read "of the mutated and/or the treated fish" to provide clear antecedent basis to the previous step. The term "and/or" is necessary to clarify that the synergy between a substance and a mutation can be measured. "and/or" should also be added at the end of line 2 of the comparing step for the same reason. At line 2 of the comparing step, the term "the" should be inserted before "model fish" to clarify that it is referring to the same model fish.

4) The claim fails to provide clear antecedent basis in the comparing step for the "aspect of behavior or physiology". The step refers to "an aspect" which could include aspects other than that caused by treatment to obtain the model fish. Thus, the step should read "comparing the aspect" and "said aspect of behavior" at line 2 of the comparing step.

Applicant is encouraged to carefully read any amended forms of the claim to ensure clear and proper antecedent basis and clarity. Removal of non-elected subject matter is encouraged to aid in clarity

of the claim. An example of more clear claim language is set forth below in the written description rejection.

Claims 31 and 32 are unclear in the use of the terms "separately" and "combination". It is also unclear if Applicant intends to use the term "and" or if the term "or" is intended. To administer the substances separately would be to give only one substance to a fish, which does not relate back to parent claim 30, which is a method of testing synergy. The specification teaches "sequentially" administering substances as well as "simultaneously" administering substances. It is also noted that "drugs" are not administered in claim 31.

Claims 39-42 are unclear. Claim 39 originally depended form claim 1 and has been amended to depend from claim 35. Claims 1 and 35 are distinct and different methods. Claim 35 is drawn to a method of assessing synergy between substances or mutations in affecting a phenotype of a fish. Claim 39 adds that a gene or mutation is identified as a wherein clause, however, this wherein clause fails to relate back to any method step of claim 35. To the extent that claims 39-42 depend from claim 35, they will be considered under the other statutes below, however, addition of any methodology to overcome the instant rejection will be considered to necessitate any future rejections and will not render an office action non-final.

Claim Rejections - 35 USC § 112-1st paragraphs

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 30-35 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter, which was not described in the

specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Vas-Cath Inc. v. Mahurkar, 19USPQ2d 1111, clearly states that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention*. The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed.*" (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See *Vas-Cath* at page 1116).

The claims are drawn to a method of testing synergy between a combination of substances and/or mutations in affecting a phenotype of a fish that is induced by administering an agent. The terminology in the claims and in the specification is inconsistent and unclear. The Examiner's interpretation of what Applicant intends to claim in light of the teachings supported by the specification is;

A method of determining whether two substances or a substance and a mutation synergistically affect the activity or effect of a treatment that alters the behavior or physiology of a fish comprising;

a) providing, as a model fish for screening, a fish subject to a treatment wherein the treatment affects an aspect of behavior or physiology of the fish;

b) subjecting said model fish to (i) mutation in combination with treatment with a test substance to provide a mutated fish or (ii) two test substances, either sequentially or simultaneously, to provide a treated fish, and

c) comparing the aspect of behavior or physiology of the mutated or treated fish with said aspect of behavior or physiology of the model fish to identify any mutation or substance combination that alters the effect of the treatment that alters the behavior of the physiology of the fish, thereby determining whether a combination of two substances or a substance and a genetic difference between the model fish and the treated or mutated fish has an additive or synergistic effect on said aspect of behavior or physiology of said model fish.

It appears that the claims, as written, are broad and lack descriptive support in two respects. First, the claims appear to fail to limit the number of substances that can be tested to synergize. However,

support in the specification is not found for more than two. Applicant is encouraged to point to specific support for such. The claims also encompass testing synergy between multiple mutations. However, the specification fails to teach testing synergy between multiple mutations. The only recitation of "two mutations" in the specification is at page 55 where one mutation is that inducing the phenotype of the fish, which is not part of the invention under examination. Support for the instant invention is found at page 23 (lines 16-20), which teaches combining a genetic mutation with a drug to determine if the mutation has a synergistic effect with the drug (substance).

Applicant is reminded that *Vas-Cath* makes clear that the written description provision of 35 U.S.C. §112 is severable from its enablement provision (see page 1115).

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 30-33 are rejected under 35 U.S.C. 103(a) as being unpatentable over Balkwill [1983, **Journal of Interferon Research**, 3:319-326] in view of Serbedzija (1999, IDS) and (Uckun, WO01/40273, published June 2001).

The claims encompass a method of determining whether two substances synergistically affect the activity or effect of a treatment that alters the physiology of a fish comprising;

a) providing, as a model fish for screening, a fish subject to a treatment wherein the treatment affects an aspect of behavior or physiology of the fish;

b) subjecting said model fish to two test substances to provide a treated fish, and

c) comparing the aspect of physiology of the treated fish with said aspect of physiology of the model fish to identify any substance combination that alters the effect of the treatment that alters the physiology of the fish, thereby determining whether a combination of two substances has an additive or synergistic effect on said aspect of physiology of said model fish.

Balkwill taught the use of a mouse model for screening and determining synergistic effects between drugs in treating tumors. Balkwill taught treating mice with tumor cells to cause tumor growth in the mice (page 320, paragraph 3), which fulfills step (a) of the claims with the exception that the step is performed in mice rather than fish. Balkwill treated the mice with alpha-interferon and interferon/drug combinations (page 320, paragraph 3; page 322, paragraph 2; paragraph bridging pages 323-324) to test for synergistic or additive effects of the compounds. To test a synergistic or additive effect of the combination one compares the effect of the combination to that of the agents individually, as claimed (see Fig. 4). Balkwill did not teach carrying out such a screen in fish.

However, Serbedzija taught fish as a model system for screening for pharmaceutical treatments of angiogenesis. The fish is a vertebrate that offers the advantage of high throughput screens (see page 358, column 1) that so far had been possible in invertebrates such as Drosophila and *C. elegans*. Furthermore, Uckun taught the use of zebrafish as cancer models in screening for drug for the treatment of cancers (Example 6).

It would have been obvious for one of skill at the time of filing to substitute the vertebrate model animal of Beckwill with that of Serbedzija and of Uckun to arrive at a model of screening synergistic interactions between treatment molecules in fish. One of skill would have been motivated to make such a substitution because the fish was established as an excellent vertebrate model of various disease that is readily used in high throughput screens.

One of skill in the art would have had a reasonable expectation of success in combining the teachings because drug screening had already bee established in fish and to test synergy between two agents merely involves treatment with an additional agent and a comparison step.

Thus, the claimed invention, as a whole, is clearly *prima facie* obvious in the absence of evidence to the contrary.

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Valarie Bertoglio whose telephone number is (571) 272-0725. The examiner can normally be reached on Mon-Thurs 5:30-4:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Peter Paras can be reached on (571) 272-4517. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Valarie Bertoglio, Ph.D./
Primary Examiner
Art Unit 1632